UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATON	**MDL No. 2606** Master Case No. 15-2606 (RBK/JS)
THIS DOCUMENT RELATES TO: ALL CASES	Hon. Robert B. Kugler U.S.D.J. Hon. Joel Schneider, U.S.M.J.

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFFS' EXPERT, DANIEL LEFFLER, M.D.

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Plaintiffs hereby file this opposition to the Defendants' Motion to Exclude the Testimony of Dr. Daniel Leffler.

INTRODUCTION AND SUMMARY OF ARGUMENT

Dr. Daniel Leffler is a board certified gastroenterologist and Director of Research at the Celiac Center at Beth Israel Deaconess Medical Center. His focus is the study and treatment of celiac disease and gastrointestinal disorders. He is an Associate Professor of Medicine at the Harvard Medical School. He has authored and edited more than 100 articles and textbooks, predominantly on celiac disease and related intestinal disorders.

In this case, Dr. Leffler has opined that olmesartan can damage the small intestine, causing malabsorption, diarrhea, abdominal pain, vomiting, weight loss and other serious gastrointestinal symptoms. The scientific literature refers to the condition caused by olmesartan as sprue-like enteropathy, olmesartan-associated enteropathy and/or olmesartan-induced enteropathy. The term "olmesartan enteropathy" will be used herein to describe the condition. Dr. Leffler's opinion is based on a thorough review of the scientific literature, his extensive clinical and research experience with celiac disease, and in treating patients with olmesartan enteropathy. This opinion was further supported by his review of a significant number of MedWatch reports documenting patients taking olmesartan, who

experienced serious gastrointestinal symptoms that improved when taken off olmesartan and reappeared when the drug was restarted (i.e. positive rechallenge).

In reaching his opinion, Dr. Leffler utilized the Bradford Hill criteria, a peer-reviewed and well-accepted methodology for determining causation. His rigorous examination of the data concerning olmesartan results in a reliable causal assessment that will assist the trier of fact through the complex scientific issues in this case. Therefore, Defendants' motion to exclude Dr. Leffler's testimony should be denied.

STATEMENT OF FACTS

Dr. Leffler is a board certified gastroenterologist specializing in diseases of the small intestine, and in particular, celiac disease. Sutton Certification[1] - Exhibit 1 - Expert Report of Daniel Leffler, M.D. at 1. As an expert in celiac disease, Dr. Leffler was particularly qualified to review the medical literature, as olmesartan's damage to the small intestine mimics that seen in celiac disease.[2] As part of his methodology, Dr. Leffler reviewed all the pertinent medical literature he could find on the topic of olmesartan enteropathy. Ex. 2 – Deposition Transcript of Daniel Leffler, M.D. at 313:15-20. Dr. Leffler's report and reference lists include hundreds

[1] Each exhibit hereafter designated, is an exhibit to the Certification of Tara Sutton filed in support of this memorandum.

[2] *See e.g.* Ex. 3 - Rubio-Tapia, Herman, et al. *Severe Spruelike Enteropathy Associated With Olmesartan*. Mayo Clin Proc. 2012 Aug;87(8):732-8 (biopsy findings "can mimic celiac disease"); Ex. 4 - da Silva, Neves, et al. *Enteropathy Associated with Olmesartan*. GE Port J Gastroenterol. 2016 Apr 30;23(2):96-100 ("Olmesartan-associated enteropathy may mimic celiac disease").

of articles. Ex. 1 at 30-33; Ex. 5 - Supplemental Reliance Lists of Dr. Leffler. His report includes a detailed chronology of nearly 70 publications, including case series, a randomized controlled trial, FDA Drug Safety Communication, retrospective analysis, nationwide cohort studies, case reports, case control studies, systemic reviews, and studies regarding the biological mechanism. Ex. 1 at 19-26. Dr. Leffler's approach to reviewing the medical literature was exhaustive and inclusive, it was not limited to only findings favorable to his opinion. Dr. Leffler concluded that:

> The medical literature…provides strong evidence that olmesartan causes enteropathy of varying severity, with associated gastrointestinal symptoms which also may range from very severe requiring prolonged hospitalization and intravenous nutritional support, to relatively mild.

Ex. 1 at 26.

In addition to the medical literature, Dr. Leffler relied on his clinical experience treating patients with celiac disease and olmesartan enteropathy, and he reviewed 62 MedWatch reports with strong evidence of rechallenge. Ex. 1 at 14; Ex. 2 at 23:13-24:4; 52-54. He found 60 of the 62 MedWatch to be "highly consistent with the cases reported in peer reviewed literature," and his review of them "support[ed] [his] conclusion that olmesartan causes enteropathy." *Id*. Based on a differential diagnosis where alternative causes were considered and ruled out, Dr. Leffler concluded that 60 of the cases "were indeed caused by olmesartan." Ex. 1. at 15; Ex. 2 at 200:17-21.

In reviewing all of the relevant data, as well as based on his clinical experience, Dr. Leffler has employed a high level of intellectual rigor and offered an opinion that rests upon good grounds that would assist the trier of fact in this case.

LEGAL ARGUMENT

I. The *Daubert* Decision is Vested in This Court's Discretion.

The Supreme Court has rejected any litmus test for admissibility, instead emphasizing that the touchstone for admissibility is "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 at 152 (1999). In forming his opinion, Dr. Leffler applies the same methods he employs in his own research and clinical work. Ex. 1 at 4, 6, 11; Ex. 2 at 263:12-264:12.

District courts enjoy "considerable leeway" when deciding whether to admit or exclude expert testimony. *Kumho*, 526 U.S. 137, 152. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking" expert testimony. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1992).

A party need not prove that the expert's opinion is correct, but rather that it rests upon "good grounds based on what is known." *Daubert*, 509 U.S. at 590. If an expert's testimony is within "the range where experts might reasonably differ," the

jury, not the trial court, should "decide among the conflicting views of different experts." *Kumho*, 526 U.S. at 153. Thus, it is well-recognized that rejection of expert testimony is to be the "exception rather than the rule." *United States v. Frazier*, 387 F.3d 1244, 1294 (11th Cir. 2004).

As the Third Circuit, "made clear in Paoli II, an expert's 'level of expertise may affect the reliability of the expert's opinion." *Elcock v. K-Mart Corp.*, 233 F.3d 734, 746 (3rd Cir. 2000) (quoting *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir. 1994) ("Paoli II")). Dr. Leffler's extensive qualifications, including treatment of patients with this injury and his familiarity with peer-reviewed literature on this subject and on celiac disease, prior to becoming an expert in the case, should bear upon the reliability inquiry. *Elcock*, 233 F.3d at 746; *Paoli II*, 35 F.3d at 741.

A recent *Daubert* opinion issued in the *In re Xarelto* MDL rejected a series of *Daubert* motions very similar to those brought by Defendants in this litigation. Judge Fallon determined that because the plaintiffs' experts applied the proper methodology, and relied on peer-reviewed literature, the balance of the defense's criticisms went to the weight of the opinions, not admissibility. *See In re Xarelto Rivaroxaban Prods. Liab. Litig., 2017 U.S. Dist. LEXIS 56628 (E.D. La. April 13, 2017)* - Ex. 6.

Courts recognize the Bradford Hill factors as, "nine factors widely used in the scientific community to assess general causation." *Glynn v. Merck Sharp & Dohm*

Corp., 213 WL 1558690 at *3, (D.N.J. April 10, 2013) (Ex. 7) ('[o]ne or more of the factors may be absent even where a causal relationship exists and…no factor is a sine qua non of causation." (citing *Magistrini v. One Hour Martinizing Dry Cleaner*, 180 F.Supp. 2d 584, 593 n. 9 (D.N.J. 2002)). Any criticism of how Dr. Leffler applied the criteria do not affect the admissibility of expert testimony, instead, the "[d]efendant is free to address these issues on cross-examination…" Ex. 7 at *4.

As discussed herein, Dr. Leffler's proposed expert testimony more than satisfies the *Daubert* standard for reliability and should be admitted. In reaching his opinions in this case, Dr. Leffler has taken into account *all* available scientific evidence, along with his own clinical experience of treating patients with olmesartan enteropathy, and his vast knowledge with respect to celiac disease. Taken together, these provide "good grounds" for his opinions.

II. DR. LEFFLER'S DESCRIPTION OF THE GASTROINTESTINAL SYMPTOMS CAUSED BY OLMESARTAN ENTEROPATHY IS WELL-GROUNDED IN THE PEER-REVIEWED LITERATURE.

Dr. Leffler testified that the common symptoms of olmesartan enteropathy are diarrhea, weight loss, abdominal pain, and vomiting. Ex. 2. at 71:10-72:2; 73:14-21. Defendants' claim that Dr. Leffler cannot define "sprue-like enteropathy" with any specificity is baseless. On the contrary, Dr. Leffler rejects the term "sprue-like enteropathy" in his report and in his deposition, because it is *too general of a term*

to accurately describe the illness caused by olmesartan. Ex. 2 at 21:18-22:7.[3] The following common symptoms have all been documented in the peer-reviewed medical literature associated with olmesartan enteropathy and may be subtle, mild, moderate, or severe: diarrhea, nausea, weight loss, abdominal pain, bloating, vomiting, fatigue, bloating, dehydration, acute kidney injury, and celiac symptoms.[4] Defendants have similarly identified the symptoms of "olmesartan induced sprue-

[3]"Sprue-like enteropathy or what we more commonly now refer to as non-celiac enteropathy just defines a class of conditions where you have small intestinal damages that's like celiac disease. One cause of sprue-like enteropathy is olmesartan enteropathy, but I don't think of those as interchangeable terms." Ex. 2 at 21:18-22:7.

[4] Ex. 8 - Choi EY, McKenna B. *Olmesartan-Associated Enteropathy, A Review of Clinical and Histologic Findings*. Arch Pathol Lab Med. 2015 Oct;139(10):1242-7 (reporting chronic diarrhea, weight loss, fatigue, nausea, vomiting, abdominal pain, and bloating as common symptoms); Ex. 9 - Fiorucci, Puxeddu, et al. *Severe spruelike enteropathy due to olmesartan*. Rev Esp Enferm Dig. 2014 Feb;106(2):142-4 (diarrhea, weight loss, dehydration, and others); Ex. 10 - Ianiro, Bibbo, et al. *Systematic review: sprue-like enteropathy associated with olmesartan*. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23 (diarrhea and weight loss); Ex. 11- Imperatore, Tortora, et al. *An emerging issue in differential diagnosis of diarrhea: sprue-like enteropathy associated with olmesartan*. Scand J Gastroenterol. 2016 Mar;51(3):378-80 (stating "though our report was characterized by a severe sprue-like enteropathy, this kind of disease can manifest even with subtle, mild, or moderate symptoms"); Ex. 12 - Marietta, Cartee, et al. *Drug-Induced Enteropathy*. Dig Dis. 2015;33(2):215-20 (symptoms include diarrhea, abdominal pain, weight loss, dehydration, acute kidney injury); Ex. 3 - Rubio-Tapia, et al. Mayo Clin Proc. 2012 Aug;87(8):732-8 (diarrhea, weight loss, nausea, vomiting, abdominal pain, bloating, and fatigue); Ex. 13 - Marietta EV, Nadeau AM. *Immunopathogenesis of olmesartan-associated enteropathy*. Ailment Pharmacol. Ther. 2015 Dec;42(11):1303-14 (stating that "olmesartan-associated enteropathy shares many features with coeliac disease, including symptoms and immunopathogenic pathways.")

like enteropathy" in deposition testimony discussing internal company documents as nausea, vomiting, diarrhea, weight and weight loss." Ex. 14 - Deposition Testimony of Tina Ho, 451:18-453:15.

In light of the signs and symptoms associated with olmesartan enteropathy reported in the peer-reviewed medical literature, Dr. Leffler's description of the possible symptoms associated with olmesartan enteropathy is appropriate. Unlike the defense experts, who have limited the potential signs and symptoms associated with olmesartan to only those listed on one table in one article published in 2012 (Ex. 3, Table 3), Dr. Leffler has considered the entirety of the medical literature in informing his opinion. He explained that "[b]ased on subsequent reports in the literature and my own clinical experience….there's a wider spectrum of presentation than was initially noted in this first 2012 article" and that the list of features on Table 3 is "not completely exhaustive." Ex. 2 at 19:1-6.

Even the authors of the 2012 Rubio-Tapia article acknowledged that the spectrum of the illness is broader than what was listed in Table 3, "[p]athologic evidence of involvement of other organs (eg, the stomach and colon) suggests that this disorder may affect the entire gastrointestinal tract." Ex. 3 at 737. Thus, Dr. Leffler's inclusion of a thorough list of symptoms associated with olmesartan enteropathy is not an attempt to "include every plaintiff on the docket," but rather

an attempt to capture the symptoms noted in the medical literature and in Dr. Leffler's experience as a clinician and celiac researcher.

Unlike the expert in *Kilpatrick v. Breg, Inc.*, Dr. Leffler did not admit in his testimony that causation was still only "hypothetical or speculative." Rather, he concluded, there is "strong evidence that olmesartan causes enteropathy of varying severity." Ex. 1 at 26. Likewise, this isn't the situation in *Pick v. Am. Med. Sys. Inc.*, where the expert's opinion was regarding symptoms "so varied and general they cannot be corralled into a specific diagnostic criteria.'" 958 F. Supp. 1151 (E.D. La. 1997).[5] The common symptoms described by Dr. Leffler are concise and find support in the medical literature, and in Defendants' own description of the syndrome.

The medical literature does not support Defendants' claim that there is a "magic" number, or combination, of symptoms required before a diagnosis of olmesartan enteropathy can be made. He testified that the common symptoms of olmesartan enteropathy are diarrhea, weight loss, abdominal pain, and vomiting. Ex. 2 at 71:10-72:2; 73:14-21.

> Many patients in many cases that I've seen with olmesartan enteropathy have these features, some or all of them, I don't think this is a

[5] Further, the Court in *Pick* excluded the testimony of the expert not because of his description of the symptoms, but because "[b]y his own, and at times proud, admission his methodology is unique to him and Dr. Deming and runs counter to the established procedures of virtually all other laboratories and medical facilities." *Pick v. Am. Med. Sys. Inc.*, 958 F. Supp. at 1178.

> completely exhaustive list of all the features of olmesartan enteropathy, and I don't think that you need all these features to be present to have olmesartan enteropathy, but I think this is a representative table.

Id. at 18:4-17. He also analogized to his experience with celiac disease, explaining that sometimes people can be "totally asymptomatic despite having significant intestinal damage leading to extraintestinal manifestations." *Id*. at 45:9-21. He went on to explain, that in the absence of symptoms, "you would need a follow-up endoscopy showing a resolution of enteropathy" to diagnose someone with olmesartan enteropathy. *Id*. at 72:20-73:3.

III. DR. LEFFLER USED A VALID METHODOLOGY FOR DIAGNOSING GASTROINTESTINAL SYMPTOMS CAUSED BY OLMESARTAN

Dr. Leffler's criteria for diagnosing olmesartan enteropathy is to observe whether a person's gastrointestinal symptoms dissipate or improve upon the withdrawal of olmesartan (positive dechallenge). Ex. 2 at 45:22-46:25; 47:11-23; 228:13-229:2. So long as there is improvement of the symptoms and *withdrawal of olmesartan is the only change made,* then olmesartan is the cause. *Id*. By requiring olmesartan withdrawal to be the only change made, other potential causes are excluded. *Id*. at 19:8-20:14; 228:13-229:2. When olmesartan withdrawal is not the only change made, then rechallenge evidence becomes useful in making a diagnosis. *Id*. at 45:22-47:10.

Dr. Leffler's diagnostic criteria of relying on dechallenge and rechallenge is a well-accepted, peer-reviewed, methodology. The FDA recognized this phenomenon when requiring a warning, as did countless other scientists publishing in the peer-reviewed medical literature. *See* Ex. 15 - 7/3/2013 Safety Communication at 3; Ex. 16 - Updated Table 10 of Hutfless Report (198 positive dechallenge cases and 22 positive rechallenge cases identified in the medical literature).[6]

These reports have a powerful role in a causal assessment. The medical textbooks and literature are replete with references to the importance of dechallenge and rechallenge. Strom's *Pharmacoepidemiology* textbook states:

> Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment.

[6]*See also* Ex. 17 - Galanopoulos, Varytimiadis, et al. *Small bowel enteropathy associated with olmesartan medoxomil treatment.* Annals of Gastroenterology. 2017;30(1):131-3 ("Physicians should be aware of this potential side effect [OAE] because suspension of the drug leads to resolution of symptoms avoiding unnecessary testing for celiac disease diagnosis and initiation of a trial gluten-free diet."); Ex. 18 - Klinge, Machicado, et al. *Olmesartan Associated Sprue-like Enteropathy: A Rare Cause of Chronic Diarrhea and Weight Loss*. Am J Gastroenterol. 2015 Oct;110(Suppl 1):S441-2 ("Recognition of olmesartan sprue is imperative as olmesartan cessation is universally effective in inducing symptoms remission"); Ex. 12 - Marietta, Cartee, et al. Dig Dis. 2015;33(2):215-20 ("Removing olmesartan, the offending agent, has been the mainstay of treatment."); Ex. 19 - Rostami, Aldulaimi, Holmes, et al. *Microscopic enteritis: Bucharest consensus*. World J Gastroenterol. 2015 Mar 7;21(9):2593-2604 ("[w]herever possible any drugs associated with ME should be stopped").

Ex. 20 - Strom BL, Chapter 3, *Basic Principles of Clinical Epidemiology Relevant to Pharmacoepidemiologic Studies*, Pharmacoepid. 86 (5th ed. 2012). Similarly, it has been stated that "[a] well-document positive rechallenge, intentional or incidental, may irrefutably prove the connection between a drug and an adverse reaction." Ex. 21- Meyboom et al, *Causal or Casual? The Role of Causality Assessment in Pharmacovigilance*, Drug Safety 1997 Dec; 17(6): 374-389 at 383. The Reference Manual on Scientific Evidence states "when such data are available and eliminating exposure reduced the incidence of disease, this factor strongly supports a causal relationship." Ex. 22 - Ref. Manual on Sci. Evid. at 605.

Thus, courts have repeatedly deemed dechallenge/rechallenge data "particularly useful in determining whether a causal relationship exists." *Rider v. Sandoz Pharmaceuticals Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002). "Rechallenge and dechallenge data is substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his prior reactions." *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001). Indeed, "[a] positive rechallenge, at least in the absence of clear evidence to the contrary, is generally considered as the strongest and most conclusive evidence that the drug is the cause of the adverse reaction." *Rolland v. Smithkline Beckman Corp.*, 1990 U.S. Dist. LEXIS 6252, at *109-10 (E.D. Pa. May 22, 1990) (Ex. 23).

Defendants mischaracterize Dr. Leffler's view of what constitutes a positive dechallenge. Dr. Leffler never said (as claimed in Defendants' brief) that "any improvement of any of the symptoms at any time after withdrawal from olmesartan transforms a potential association into a cause-effect relationship, regardless of other potential causes of the condition." Defs' Brief at 12. What he actually said was that there must be an "improvement of symptoms," and that it "often takes months," and that "while you would expect in the majority of cases to see some response within the first few months, maybe even weeks, in some cases it can reasonably take longer…." Ex. 2 at 55:12-56:9; 61:11-64:13. This is in line with the FDA, which defines dechallenge as "partial or complete disappearance of an adverse event after withdrawal of the drug." Ex. 24 - FDA's Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, at 35 (emphasis added). And, it is in line with the peer-reviewed medical literature, which reports that the level of improvement following withdrawal of olmesartan can be partial, and can take a variable amount of time.[7] Thus, Dr. Leffler's testimony is consistent with the medical literature.

[7] *See e.g.* Ex. 10 - Ianiro, Bibbo, et al. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23 (improvement, but not total resolution two months after olmesartan discontinuation); Ex. 25 - Machado, Reolid, et al. *Sprue-like enteropathy associated with olmesartan in a patient with villous atrophy, HLA-DQ2 genotype and antinuclear antibodies*. Rev Esp Enferm Dig. 2016;108(11):732-3 (symptoms requiring treatment persisted after eight weeks of olmesartan cessation); Ex. 26 - Scialom, Malamut, et al. *Gastrointestinal Disorder Associated with Olmesartan*

Dr. Leffler did not state, as Defendants assert, that "objective evidence is not required to rule out other causes or pin the cause on olmesartan." Def Brief p. 12. In actuality, Dr. Leffler testified that in instances where positive dechallenge is not clear, objective evidence like biopsy results can be helpful in ruling out other disorders. Ex. 2 at 75:8-22. Defendants' claim that "a patient need not actually improve in order for [Dr. Leffler] to diagnose "olmesartan enteropathy" is likewise not supported by the testimony.

Defendants cite *Turner v. Iowa Fire Equip. Co.*, for the proposition that "[a]necdotal approaches to evaluating causation are not reliable bases upon which to ground expert opinions." 229 F.3d 1202 (8th Cir. 2000). But Dr. Leffler's approach is not anecdotal. The fact that numerous peer-reviewed publications have concluded—like Dr. Leffler—that olmesartan enteropathy can be diagnosed using dechallenge and rechallenge, establishes that Dr. Leffler's opinion relies upon "good grounds" and is supported by "appropriate validation." *Daubert*, 509 U.S. at 590.

Mimics Autoimmune Enteropathy. PLoS One. 2015 Jun 23;10(6):e0125023 (symptoms remaining more than six months after cessation).

IV. DR. LEFFLER'S DEFINITION OF THE PERIOD OF EXPOSURE NECESSARY FOR SYMPTOM MANIFESTATION IS WELL FOUNDED.

Peer-reviewed medical articles describe a varied latency period associated with olmesartan enteropathy – ranging from a few weeks to many years.[8] In his report, Dr. Leffler opined that there can be "significant variability in time to onset of olmesartan enteropathy," which is fully supported by the peer-reviewed medical literature, as well as his clinical experience. Ex. 1 at 26. In his deposition, he explained that "…I think that an immune reaction like this needs to develop. It shouldn't happen on the first exposures…they have to have some time of initial exposure in order to develop the disease." Ex. 2 at 51:14-52:11. When asked if ten years of exposure would be too long of a latency period, he analogized to his experience treating patients with celiac disease, "I think as long as there's continued exposure to the drug, there is no – there's no time at which it is not possible to develop that." *Id*. at 51:14-54:16 (noting patients can develop celiac disease in their 60s, 70s, or 80s, despite eating gluten their entire lives). Defendants characterize Dr.

[8]Ex. 27 - Famularo G, Minisola G. *Relapsing Olmesartan-Associated Ileitis*. Ann Pharmacother. 2016 Dec;50(12):1070. Epub 2016 Aug 18 (symptoms appearing after 2 weeks); Ex. 25 - Machado, Reolid, et al. Rev Esp Enferm Dig. 2016;108(11):732-3 (symptoms appearing after 5 ½ years); Ex. 3 - Rubio-Tapia, Herman, et al. Mayo Clin Proc. 2012 Aug;87(8):732-8 (seven years until symptom onset for at least one patient).

Leffler's opinion as "contrary to" the 2012 Mayo article, however, the time to onset of symptoms in that article ranged from six months to seven years.

V. DEFENDANTS' CLAIM THAT DR. LEFFLER'S OPINION IS LITIGATION DRIVEN IS FALSE.

It was **years before** being retained as an expert in this case that Dr. Leffler first learned of a potential association between olmesartan and enteropathy, after reading a 2010 Mayo Clinic article. Ex. 2 at 28:10-29:2. Upon reading the subsequent Mayo Clinic case series by Dr. Murray published in 2012, Dr. Leffler understood that this was an "independent clinical condition." *Id*. at 27:10-29:11. Alarmed, Dr. Leffler's research associates went back and found cases of potential olmesartan enteropathy in a study population of refractory celiac disease patients. *Id*. at 98:11-99:8. In 2013, his clinic undertook a re-contact effort, sending letters to patients who had taken olmesartan, warning them of this issue. *Id*. at 99:6-100:19. Dr. Leffler's opinion that olmesartan causes enteropathy was therefore initially formed as a result of reading the available scientific record at the time, as well as his own clinical experience. This is not a litigation-driven opinion.

Unlike the expert in *Claar*, who wrote his opinion "prior to reviewing any of the relevant literature," Dr. Leffler did a literature review after being contacted to serve as an expert, and before writing his report. Ex. 2 at 140:14-141:7. Were the court to accept this argument from Defendants, any expert with actual experience treating a condition caused by a drug, who had accepted the causal relationship

between that drug and injury as part of their medical practice, would be ineligible to serve as an expert. Under *Daubert*, an indicia of reliability includes whether an expert is, like here, "proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation." *Daubert*, 43 F.3d at 1317 (9th Cir. 1995). It is not Dr. Leffler who developed his opinions expressly for the purpose of testifying, but rather Defendants' experts, many of whom had never heard of sprue-like enteropathy, or olmesartan enteropathy, prior to being hired.

VI. DR. LEFFLER DID NOT SPECULATE ABOUT UNDERDIAGNOSIS OR MISDIAGNOSIS OF OLMESARTAN ENTEROPATHY.

Ignoring the large quantity of peer-reviewed medical literature to the contrary, Defendants claim that there is no support for Dr. Leffler's opinion that olmesartan enteropathy has been misdiagnosed as celiac disease, or has been underdiagnosed. This contention simply ignores reality. For example, a 2013 article describing 72 patients who had been referred to a center after having been diagnosed as having poorly responsive/refractory celiac disease reported that sixteen of the patients were later diagnosed with olmesartan induced enteropathy. Ex. 28 - DeGaetani, Tennyson, et al., *Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma,* Am J Gastroenterol. 2013 May;108(5);637-53 (emphasis added). Numerous other case reports tell the same story – patients diagnosed with celiac, or some other gastroenterological disease, who are ultimately found to have been

misdiagnosed and who actually had olmesartan enteropathy.[9] Likewise, there are peer-reviewed articles which support Dr. Leffler's opinion that olmesartan enteropathy is underdiagnosed.[10]

Further, Dr. Leffler noted that "[o]lmesartan enteropathy, in my practice, was often misdiagnosed" as celiac disease or other bowel disease, and that he had himself misdiagnosed olmesartan enteropathy. Ex. 1 at 3; Ex. 2 at 98:11-99:8 and 124:20-125:1. The inadequate labeling regarding the risk of olmesartan enteropathy contributed to the potential underdiagnosis/misdiagnosis of this condition. Ex. 2 at 87:19-88:22; 265:7-268:3 These opinions are grounded firmly in Dr. Leffler's

[9] *See e.g.* Ex. 29 - Carneiro, Moreira, *Olmesartan-Induced Sprue Like Enteropathy*. GE Port J Gastroenterol. 2016 Apr 30;23(2):101-5 (olmesartan enteropathy misdiagnosed as lymphocytic colitis); Ex. 9 - Fiorucci, Puxeddu, et al. Rev Esp Enferm Dig. 2014 Feb;106(2):142-4 (misdiagnosed with viral gastroenteritis); Ex. 30 - Hartranft, Regal. '*Triple Phase' Budesonide Capsules for the Early Treatment of Olmesartan-Induced Enteropathy*. Ann Pharmacother. 2014 Jun 23;48(9):1234-37 (misdiagnosed with autoimmune enteropathy); Ex. 31 - Khan, Peter, Wilcox. *Olmesartan-induced enteropathy resembling celiac disease*. Endoscopy. 2014;46 Suppl 1;E97-E98 (misdiagnosed as celiac disease).

[10] *See e.g.* Ex. 32 - Desruisseaux, Bensoussan, et al. *Adding Water to the Mill: Olmesartan-Induced Collagenous Sprue – A Case Report and Brief Literature Review*. Can J Gastroenterol Hepatol. 2016;2016:4837270 (noting "[t]his condition is likely to be underreported."); Ex. 33 - Eusebio, Caldeira, et al. *Olmesartan-Induced Enteropathy: An Unusual Cause of Villous Atrophy*. GE Port J Gastroenterol. 2016 Apr 30;23(2):91-5 (concluding "this report intends to alert the clinical community for this probably underreported problem").

clinical experience, and the medical literature, and are therefore not "speculation, but rather demonstrate his valid methodology."[11]

VII. DR. LEFFLER PROPERLY ASSESSED THE EPIDEMIOLOGICAL DATA IN REACHING HIS GENERAL CAUSATION OPINION.

Dr. Leffler did an exhaustive review of all of the medical literature in formulating his opinions in this case, including a review of all of the epidemiological evidence. He concluded in his report that "[t]he medical literature provides robust evidence that there is a causal connection between olmesartan and enteropathy with gastrointestinal symptoms and malabsorption. Different studies in a variety of populations have consistently found evidence of olmesartan related gastrointestinal toxicity." Ex. 1 at 19. Dr. Leffler did not "ignore" or "discard" any of the epidemiology available. Rather, he took it all into account, and evaluated the merits of each of the studies to determine how much weight to place on each. Therefore, Dr. Leffler's approach does not suffer from the same flaws as the expert in *Lust By & Through Lust v. Merrell Dow Pharmaceuticals*, cited by Defendants. 89 F.3d 594, 596 (9th Cir.1996). Indeed, "the accepted scientific practice is for an expert to

[11] Defendants' citation to *In re Baycol Prods. Litig.* does not support their argument. The *Baycol* expert was offering testimony as to other physician's knowledge, and what the other physicians would have done with different information. The *Baycol* expert had no medical literature to support his opinion. Here, Dr. Leffler, is testifying about the misdiagnoses and underdiagnoses noted in the peer reviewed medical literature, and about which he has firsthand experience.

explain why she gives more weight to certain studies in forming her opinion, discussing methodology, power, and other key factors." *In re Zoloft (Sertraline Hydrochloride) Products Liab. Litigation*, 26 F.Supp.3d 449, 461 (E.D. PA 2014). See also, *In re Avandia Marketing, Sales Practices & Products Liab. Litigation*, 2011 WL 13576, *9 (Jan. 4, 2011) ("When he rejects research that does not support his opinion, he explains why he finds that research flawed and not compelling…[H]is approach to the data was scientifically reliable. Any inconsistency…[or] any flaws in his conclusions, go to weight, not admissibility."). Ex. 34.

Most well-respected and prestigious scientific bodies reject the "atomization of evidence" approach utilized in Defendants' brief. Rather, consideration should be given to "all relevant available scientific evidence, taken as a whole, to determine which conclusion or hypothesis regarding a causal claim is best supported by the body of evidence." Ex. 22 at 20.[12] Defendants' "atomized" attack on the

[12] *See also Milward v. Acuity Specialty Products Group*, 639 F.3d 11, 31-31 (1st Cir. 2011) (*cert. denied*) (admissibility of expert testimony cannot not be determined by examining pieces of individual evidence one-by-one.); *United States v. W. R. Grace*, 504 F.3d 745, 765 (9th Cir. 2007) (court's "document-by-document Rule 702 analysis that deconstructed the experts' testimony in a manner not contemplated by Rule 702" found erroneous); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003) ("Defendants isolate these sources, rather than considering the whole."); *Rider v. Sandoz Pharmaceutical Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002) (case reports "may support other proof of causation.").

epidemiological evidence underlying Dr. Leffler's opinion thus should be rejected on its face.

A. The Basson Study

In 2015, an article was published describing a review of the French National Health Insurance claim database.[13] The study examined the rates of hospitalization for intestinal malabsorption and celiac disease in patients on angiotensin receptor blockers (ARBs) and those on angiotensin converting enzyme inhibitors (ACEIs). Ex. 35. It found that "olmesartan users were found to have an increased risk of hospitalisation for intestinal malabsorption and coeliac disease compared with ACEI. These risks increased with duration of olmesartan exposure up to 10-fold beyond 2 years of exposure." *Id*. The study included more than 4.5 million patients and was very robust.

Defendants complain that this peer-reviewed study is "susceptible to bias," identifies a "very small incidence" of malabsorption, and did not control for concurrent medications. Def. Brief at 16. The Basson article does indeed discuss possible biases, but finds that the biases likely do not affect the results, except that "this study underestimates the true incidence and only provides the incidence of the most severe forms of olmesartan-associated enteropathy." Ex. 35 at 5. While

[13]Basson, Mezzarobba, et al. *Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study*. Gut. 2015 Aug 6. pii: gutjnl-2015-409690 – Ex. 35.

controlling for concurrent medications was not done, other confounder controls were utilized, including adjusting for comorbidities such as immune-mediated abnormalities, patients with diagnosis likely to be prescribed drugs that provoke diarrhea, and patients with other diseases that commonly cause diarrhea. *Id.* at 2-3.

Defendants' litigation-driven view of Basson is not shared by the scientific world. Indeed, this study is described in the literature as being "well-conducted" and "puts to bed any controversy surrounding the association between the ARB olmesartan and severe intestinal enteropathy pathologically resembling celiac disease." Talley NJ, *Use of olmesartan for ≥ 1 year was associated with hospitalization for intestinal malabsorption,* Ann Intern Med. 2015 Dec 15;163(12):JC13. doi: 10.7326/ACPJC-2015-163-12-013 - Ex. 36. The Basson study has been complimented for its rigor, "[s]urrogate diagnoses for olmesartan enteropathy were used to search the database, selection bias was minimized, and confounding was carefully considered." *Id.*

B. The ROADMAP Study

Curiously, Defendants criticize Dr. Leffler's treatment of ROADMAP, though their own expert finds it of no value in assessing causation. Ex. 37 - Risch Dep. at 283:2-11. As Dr. Leffler testified, "the ROADMAP study was not a study designed to look for olmesartan enteropathy. It was designed to look at diabetes outcomes." Ex. 2 at 286:2-15. The diabetic patient population which was studied in

ROADMAP has high rates of gastrointestinal complaints, which could have confounded the results, making the study unreliable. *Id.* at 287:14-289:20. (Defendants' expert, Harvey A. Risch, agreed. Ex. 37 at 318:2-22.) Even the investigators for the study acknowledged that the study could be underpowered to identify what they termed a likely rare adverse event. See Menne, Haller, *Olmesartan and Intestinal Adverse Effects in the ROADMAP Study*, Mayo Clin Proc. December 2012;87 (12):1230-1232 - Ex. 38.

Dr. Leffler's view of the ROADMAP study was confirmed by an olmesartan enteropathy case from ROADMAP that went undetected by Defendants or the study authors, even on reanalysis years later. Ex. 1 at 16. That case involved a woman who had treated with olmesartan as part of the ROADMAP clinical trial for around 11 months when she developed "gastroenteritis" and hypokalemia. *Id.* Olmesartan was discontinued and her symptoms resolved within about a month. *Id.* A few days after her symptom resolution, she was reintroduced to olmesartan, whereupon her symptoms (diarrhea, dehydration, hypokalemia and hypocalcemia) returned within a few days (positive rechallenge). *Id.* The symptoms continued for several weeks until olmesartan was again stopped. *Id.* The failure of the retrospective analysis of the ROADMAP data to identify such a clear case of olmesartan enteropathy supports that fact that ROADMAP is not helpful in addressing causation.

The existence of this ROADMAP case report, however, does not mean that ROADMAP was powered to detect olmesartan enteropathy. Defendants' argument to this effect demonstrates a complete misunderstanding of the concept of "power." The point made by Dr. Leffler – and agreed to by Defendants' – was that ROADMAP simply did not include a sufficient number of patients to detect any significant difference between the rate of olmesartan enteropathy in the olmesartan arm versus the placebo arm. Ex. 2 at 280:15-281:8; Ex. 39 - Hutfless Rept. at 29-30; Ex. 55 – Deposition Testimony of Richard Hanson at 67:8-68:21. Thus, as Dr. Leffler testified, while "…randomized controlled trials are… excellent for interpreting the primary outcome of the study. For secondary outcomes and adverse events, they are often insufficient. And this is why we do things like MedWatch reports." Ex. 2 at 282:5-20.

C. The Greywoode Study

The Greywoode case control study looked at 14,516 patients, of which "only 105 patients studied had been exposed to olmesartan." Ex. 1 at 23; Ex. 2 at 296:24-298:9. As Dr. Leffler's report makes clear, he did not "ignore" or "discount" the results of the study, in fact he included a description of the findings in his report, where he noted that the study authors themselves wrote that the "small prevalence of use of olmesartan (0.7%-1%) among study patients, limit[ed] the power of this analysis." Ex. 1 at 23. Other peer-reviewed publications reached the same

conclusion: "The [Greywoode] study was limited, however, by the small number of patients taking olmesartan." Ex. 8.

Dr. Lebwohl, one of the authors of the Greywoode study, testified in his deposition that "this exposure [to olmesartan] wasn't very common in either group, which really limited our ability to draw firm conclusions." Ex. 40 - Lebwohl Dep. 145:22-146:1. He went on to say that the study did actually conclude that "causality had been established." Ex. 40 at 146:2-24. Defendants' expert, Dr. Risch, also testified that the Greywood study was underpowered and the terminology used for the outcome was not sufficiently specific to measure olmesartan enteropathy. Ex. 37 at 307:16-308:7.

D. The Lagana Study

In one breath Defendants claim Leffler "swept aside" the findings in the Lagana study,[14] and then in the next, criticize him for acknowledging certain findings in that study. Def's Brief at 21-22. The Lagana study involved a handful of patients who presented for endoscopies at Columbia with a complaint of abdominal pain. Ex. 41. Very few of those patients were actually taking olmesartan, and as the study authors admitted, "[a] larger sample size may have been useful, as it is possible that olmesartan causes a true increase in duodenal histopathological abnormalities

[14]Ex. 41 - Lagana S., *Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers.* J. of Clin. Path. at 29-32 (2015).

but that our study was underpowered to detect this effect." *Id.* The peer-reviewed literature had similar criticisms. Ex. 8 ('[t]his study, however, was limited by small sample size and lack of follow-up." *Id.* at 1243.)

Dr. Leffler did not "rely" on the trend in the Lagana article, he simply noted its existence, as have others in the peer-reviewed literature. See Ex. 8 at 1243. This case is therefore immediately and easily distinguishable from *Caraker v. Sandoz Pharms, Corp.*, 188 F. Supp. 2d 1026, 1033-34 (S.D. Ill. 2001), cited by Defendants.

E. The Padwal Study

There is no question that Dr. Leffler considered the Padwal Study in reaching his opinions. He noted its lack of statistical significance but also saw a trend in the study data that showed an increase in gastrointestinal disease-related hospitalizations associated with olmesartan. Ex. 2 at 308:5-310:22. Dr. Leffler also correctly points out that the duration of exposure in Padwal was not long enough to really begin seeing severe outcomes. *Id.* at 309:14-310:2. As Basson showed, the risk of developing olmesartan enteropathy increases over time. Defendants' brief describes the study as having "maximum follow-up period of six years," but neglects to note that the "median duration" of follow up was only 2.3 years. Ex. 42 – Padwal Study at 979. Of note, Defendants' expert, Dr. Risch, also found Padwal of little value, testifying that the background rate of gastrointestinal events may have masked the effect of olmesartan, and also concluding that the events measured were not "specific

enough" to detect olmesartan enteropathy in the population studied. Ex. 37 at 313:8-14; 318:2-22.

F. Dr. Leffler Reviewed the Totality of the Evidence.

Dr. Leffler's review of the epidemiological evidence was thoughtful and complete. During his deposition, Dr. Leffler explained that:

> …the Basson study was the only one of these studies with significant enough power and duration to detect a difference. In the other studies, many of them show a trend, although it does not reach statistical significance, and that is exactly what you would expect to see…when you look at studies that aren't powered to detect [a certain outcome].

Ex. 2 at 312:19-313:2. Dr. Leffler's review of the epidemiology is not litigation or results-driven, nor did he "ignore" any studies that didn't support his opinion. Rather, he took all of the studies into account, noting their limitations. Consideration should be given to "all relevant available scientific evidence, taken as a whole, to determine which conclusion or hypothesis regarding a causal claim is best supported by the body of evidence." Ex. 22 at 20.

Of course, *Daubert* anticipates there may be science on both sides of an issue. The Supreme Court has recognized that there is a range within which experts might reasonably differ on issues of science, and that such conflicting evidence should be admitted to the jury. See *Kumho Tire Co.*, 526 U.S. at 153. In contrast to Defendants' experts, who relied upon a subset of the epidemiological studies, and ignored the compelling dechallenge/rechallenge MedWatch reports, Dr. Leffler's review

included all types of studies, regardless of their findings. Moreover, the fact that certain studies might reach a "contrary conclusion," goes to the weight, not the admissibility of the testimony. See e.g. *Souther v. Eli Lilly & Co. (In re Zyprexa Prods. Liab. Litig.)*, 489 F. Supp. 2d 230, 285 (E.D.N.Y. 2007).

VIII. DR. LEFFLER'S DOSE-RESPONSE TESTIMONY IS SUPPORTED BY PEER-REVIEWED MEDICAL LITERATURE

Dr. Leffler addressed all the Bradford-Hill factors, including the factor of dose-response. He wrote that "overall risk increases with duration of use," and described a potential "cumulative dose effect." He further noted that the "lack of differential risk of olmesartan enteropathy by daily dose suggests that all clinical regimens are above the threshold for reactivity." Ex. 1 at 13.

Defendants challenge Dr. Leffler's opinion that "the risk of olmesartan enteropathy increases with duration of exposure to olmesartan," alleging that Dr. Leffler can't "define the timeframe for this putative increased risk." However, the Basson study supports Dr. Leffler's position, stating, "t]hese risks [of olmesartan enteropathy] increased with duration of olmesartan exposure up to 10-fold beyond 2 years of exposure." (Emphasis added.) Ex. 35. In light of this strong epidemiological evidence, Dr. Leffler's statement is not "speculation."

Defendants also characterize Dr. Leffler's description of how a second environmental trigger may explain the latency period as a "guess." But Dr. Leffler's report explains that this phenomenon, "[t]his need for a 'second hit,' where an

individual is predisposed to an inflammatory condition but does not manifest it until the immune system is primed by a secondary stimuli such as infection or stress, is common in allergy and autoimmunity." Ex. 1 at 13. The peer-reviewed medical literature fully supports Dr. Leffler on this point, as does Dr. Leffler's experience treating people with celiac disease.[15] Ex. 2 at 52-54.

Even if Dr. Leffler had failed to opine on dose-response, or if his opinion were found to be "speculative," dose-response is not, as Defendants claim, an "essential" feature of the Bradford Hill method for assessing causation." *Carl v. Johnson & Johnson*, cited by Defendants, never defines dose response as "essential." 2016 N.J. Super. Unpub. LEXIS 2102 (Sup. Ct. N.J. Sept. 2016). Ex. 45. As the Reference Guide on Epidemiology establishes, dose-response is simply one factor in a causal assessment, and is "not essential." Ex. 45 at 599-600, 603. Indeed, it is generally accepted that not all drugs which cause a particular side effect exhibit a dose-response relationship. *Id.* at 603. And, the lack of a dose-response is not inconsistent with a causal relationship. *Id.*

[15]Teruel M, Alarcon-Riquelme ME. *The genetic basis of systemic lupus erythematosus: What are the risk factors and what have we learned.* J Autoimmun. 2016 - Ex. 43 and Lebwohl B, Murray JA, et al. *Gluten Introduction, Breastfeeding, and Celiac Disease: Back to the Drawing Board*. Am J Gastroenterol 2016;111:12-4 - Ex. 44; Schiepatti A, Biagi F, et al. *Olmesartan-associated enteropathy: new insights on the natural history? Report of two cases.* Scand J Gastroenterol 2016;51:152.6 – Ex. 46.

For that reason, numerous courts in drug product liability cases have not required dose-response evidence. *McClain v. Metabolife Int'l, Inc*., states that "[o]ne should not conclude . . . that to pass Daubert muster an expert must give precise numbers about a dose-response relationship. Some ambiguity about individual responses is expected." *McClain*, 401 F.3d 1233, 1241 n.6 (11th Cir. 2005).[16]

IX. DR. LEFFLER'S MECHANISM OF ACTION OPINION IS WELL SUPPORTED AND RELIABLE.

Dr. Leffler has written, researched, and lectured extensively on the pathogenesis – biological mechanism – of gastrointestinal illness and disease. Ex. 1 at 1-2 (report); 6, 7, 17-19, 22-23, 29 (Curriculum Vitae), Ex. 2 at 160:21-162:10.

[16] *See also, e.g., In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 612 F. Supp. 2d 116 (D. Mass. 2009) (denying motion to exclude plaintiffs' general causation experts' opinion that Neurontin can increase risk of suicide without determination of dose-response relationship); *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164 (S.D.N.Y. 2009) (denying motion to exclude plaintiffs' general causation experts' opinion that drug can cause osteonecrosis of the jaw without requiring demonstration of toxic dose); *Bartlett v. Mutual Pharmaceutical Company, Inc*., 759 F. Supp. 2d 171 (D.N.H. 2011) (denying motion for judgment as a matter of law because plaintiff presented sufficient evidence that drug's risks outweighed its benefits without discussion of toxic dose); *In re Zicam Cold Remedy Mktg., Sales Practices, and Prods. Liab. Litig*., 797 F. Supp. 2d 940, 945-946 (D. Ariz. 2011) ("Plaintiffs need not provide precise information concerning the exposure necessary to cause specific harm to humans… A qualitative, rather than quantitative, analysis can suffice."); *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, 2011 U.S. Dist. LEXIS 3961, 2011 WL 13576 (E.D. Pa. 2011) (denying motion to exclude plaintiffs' general causation experts' opinion about causal connection between Avandia and myocardial infarction without discussion of toxic dose) - Ex. 34.

Thus, he is certainly qualified to opine on the plausible biological mechanism by which olmesartan causes enteropathy:

> In olmesartan enteropathy, as with celiac disease, it is clear that there is a profound increase in cytotoxic CD8+ T cells, which together with granzyme B+ cells are the main mediators of damage to the intestinal epithelium. Olmesartan also appears to increase expression of IL15 and IL15R, which are key regulators of intestinal immune function….This immune activation leads to the increase in intraepithelial lymphocytes and villous destruction seen in olmesartan enteropathy…..

Ex. 1 at 12-13 (internal citations omitted). His opinion is based in part on the groundbreaking work of the Mayo Clinic, which first identified olmesartan enteropathy, and other articles in the peer-reviewed literature,[17] as well as his experience with celiac disease, immunology and pathophysiology. Ex. 2 at 162:5-9. "[O]lmesartan, either acting alone or in conjunction with another protein…is able to activate IL-15 as part of the innate immune system….By increasing IL-15, you produce an enteropathy." Ex. 1 at 175:3-176:5. The fact that scientific publications match Dr. Leffler's opinion shows it rests upon "good grounds," supported by "appropriate validation." *Daubert*, 509 U.S. at 590.

It is not necessary that Dr. Leffler's mechanism be absolutely proven. A biological plausibility opinion is admissible as long as it is coherent with existing knowledge. *In re Zicam Cold Remedy Mktg, Sales Prac. & Prods. Liab*. 2011 U.S.

[17] Ex. 13; Ex. 47 - Jabri B, Abadie V. *IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction.* Nat Rev Immunol 2015;15:771-83; Ex. 28; Ex. 3; Ex. 10.

Dist. LEXIS 20356, *110-112 (D. Ariz. Feb. 23, 2011) - Ex. 48. The test is not whether the theory is proven correct. *Id.* (citing Reference Manual on Scientific Evidence at 375-78). Thus, "the fact that an expert does not use absolute terms but rather couches the opinion in terms of 'can' or 'may' does not render it speculative or unreliable." *In re Trasylol Prods. Liab. Litig*., 2010 U.S. Dist. LEXIS 52408, *150-51 (S.D. Fla. 2010) - Ex. 49.

Defendants embark on a haphazard effort to distinguish the medical literature supporting Dr. Leffler's opinion on biological mechanism. Defendants point out that the authors of the Marietta paper "noted multiple limitations to their study and the need for 'further analysis,'" but in the same paragraph admit that the Marietta paper supports Dr. Leffler's mechanism opinion that there is an "increased IL-15 expression in some olmesartan patients." Defs.' Brief at 29. Defendants' cling to the fact that in Marietta, the increase in IL-15 expression was only in the epithelium, and not in the lamina propria, which Defendants claim is necessary in celiac related villous atrophy. *Id.* at 29, 32. However, Dr. Leffler explained that "in celiac disease you see cases where IL-15 levels are increased only in the epithelium." Ex. 2 at 176:10-24.

Dr. Leffler opines that an increase in IL-15 expression leads to a destructive T cell response. Defendants claim that the "'destructive' T cell response side of this equation…has no support in the scientific record relating to olmesartan" and that Dr.

Leffler inappropriately relies on celiac literature. Defs.' Brief at 32. But olmesartan enteropathy is commonly compared to celiac disease in the peer-reviewed literature.[18] Moreover, Marietta actually found a destructive T cell response. There was a "significant increase ($p < 0.05$) in the number of CD8+ cells in the duodenum of OAE [olmesartan associated enteropathy] patients on the drug as compared to off the drug." Ex. 13 at 3. CD8+ cells "are cytotoxic…they're responsible for damaging the…cells, for attacking other cells." Ex. 2 at 170:10-171:3.

Defendants attempt to discount Scialom et al.[19] and Malamut[20] by noting the words "remains to be elucidated" appear in the articles. This argument fails. Both Scialom and Malamut offer evidence of a plausible biological mechanism, which support the mechanism advanced by Marietta. Furthermore, the biological mechanism to be considered need only be plausible, it does not need to be definite. *Wells v. Ortho Pharmaceutical Corp.*, 788 F.2d 741, 745 (11th Cir. 1996).[21]

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[18] See note 2, *supra*.

[19] Ex. 26.

[20] Ex. 50 - Malamut G, Cerf-Bensussan N, Cellier C. *Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy*. Expert Rev Gastroenterol Hepatol 2015;9:719-21.

[21] *Glastetter*, 252 F.3d 986, 989-900 (8th Cir. 2001), cited by Defendants, is easily distinguishable as the expert there "failed to produce scientifically convincing evidence that [the drug] causes vasoconstriction." This is hardly the case with olmesartan and enteropathy, where there is a large volume of scientific evidence supporting a causal link.

Defendants argue that Dr. Leffler "ignores findings that counter [his] conclusions – for example, no increase in granzyme b positive cells and an increase in FoxP3 cells." This is an incorrect statement, Dr. Leffler did not ignore these findings, rather he took them into account:

> Q. Okay. And in your report, you did not include that fact that they did not find a statistically significant increase in granzyme B positive cells, correct?
> ….
> A. That is correct. I don't think in all cases you can equate statistical significance with clinical or pathophysiologic importance.

Ex. 2 at 171:16-23. Dr. Leffler explained that an increase in FoxP3 cells (which have a role of trying to "balance out inflammatory conditions") could simply be one pathway for "unchecked inflammation." *Id.* at 172:6-173:8. When there is so much "proinflammatory medias that it overwhelms the ability of the T regulatory cells to balance that out…[The increase in FoxP3 cells] just is a suggestion of the body's inability to respond and adapt with whatever is triggering the inflammation." *Id.* Dr. Leffler did not ignore data indicating that olmesartan had anti-inflammatory and anti-fibrogenic qualities. He testified, "[i]t's widely known that medications can have vastly different effects in different organs….Anti-inflammatory drugs are a great example, NSAIDs, that reduce inflammation in your joints but cause inflammation in your intestine." *Id.* at 194:5-12

Dr. Leffler thus relied upon peer-reviewed medical literature and his expertise derived from years of treating and studying patients with small bowel disease. This methodology is well established and reliable. *McClain v. Metabolife Int'l, Inc*., and *Doe v Ortho-Clinical Diagnostics, Inc*., referenced by Defendants, do not hold otherwise.[22] In *McClain,* the district court had "disavowed its ability to handle the Daubert issues," stating that it could not "cope in this case" because it lacked a scientific background. *Id.* at 1238, n.3. The Eleventh Circuit found that this "abdication" warranted reversal of the district court's admission of expert testimony on causation. *Id.* at 1238. The experts in *McClain* and *Doe* offered no epidemiological data in support of their opinions, and further failed to review the case reports in a reliable way. This is not so with Dr. Leffler, who referred to multiple sources, including epidemiology, cohort or observational studies, a large number of case reports, and dozens of well documented rechallenges reported in the MedWatch forms.

X. DR. LEFFLER'S RELIANCE ON REPORTS OF POSITIVE DECHALLENGE AND RECHALLENGE WAS PROPER.

Case reports are part of the empirical evidence an expert may consider when examining the relationship between an adverse event and a particular agent. Use of case reports to support causation is reliable and accepted methodology. Among the

[22] *McClain*, 401 F.3d 1233, 1245 (11th Cir. 2005); *Doe,* 440 F. Supp. 2d 465, 472-76 (M.D. N.C. 2006).

case reports of olmesartan enteropathy are many cases showing the dechallenge and rechallenge relationship between olmesartan use and severe gastrointestinal injury. These reports have a hallowed role in a causal assessment. "Rechallenge and dechallenge data is substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his prior reactions." *Glastetter*, 252 F.3d at 990. Indeed, dechallenge/rechallenge data have been considered a type of "controlled study" that are "particularly useful in determining whether a causal relationship exists." *Rider,* 295 F.3d at 1199. See also, Ex. 51 - U.S. Dept. of Health and Human Services, Food and Drug Administration Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiolgic Assessment 4 (March 2005) ("It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge.")

In many instances, the MedWatch reports reviewed by Dr. Leffler describe patients who experience severe gastrointestinal symptoms while on olmesartan that abate when taken off the drug, only to have them reappear when olmesartan is resumed, i.e., rechallenge. Ex. 1 at 16. There are numerous published case reports and case series describing this type of rechallenge,[23] including the seminal 22 patient case series published by Mayo Clinic in 2012, which involved four rechallenges. Ex.

[23] *See* Ex. 16 - (198 positive dechallenge cases and 22 positive rechallenge cases identified in the medical literature).

3. Peer-reviewed medical literature and epidemiological textbooks agree that rechallenge information is a reliable source of information for determining causation. See e.g., Ahmad et al., Spontaneous Reporting in the United States in Pharmacoepidemiology 135, 152 (Brian L. Strom, ed., 4th ed. 2005) - Ex. 52.

Defendants' authorities suggesting the impropriety of utilizing case reports for determining causation are all distinguishable. The expert in *Brumbaugh v. Sandoz Pharm Corp.*, presented no epidemiological or other evidence which showed a causal link between the drug and the alleged injury. 77 F. Supp. 2d 1153 (D. MT 1999). The expert relied on case reports which were "generated through other litigation." *Id.* In the case of olmesartan, there is epidemiology showing a causal connection, in addition to numerous studies and case reports documenting rechallenge, which are not litigation generated, all of which support causation. Dr. Leffler's opinions were formed based on the peer-reviewed medical literature, his clinical experience treating olmesartan enteropathy, and his knowledge of celiac disease. His review of the MedWatch reports "support[ed his] conclusion that olmesartan causes enteropathy." Ex. 1 at 14.

DeLuca v. Merrell, Ervin v. Johnson & Johnson, and Siharath v. Sandoz Pharms. Corp., cited by Defendants, are factually distinguishable from this case.[24]

[24] *DeLuca*, 791 F. Supp. 1042 (D. NJ. April 1992); *Ervin*, No. 2:04-cv-0205, 2006 WL 1529582 (S.D. Ind. May 30, 2006), *aff'd* 492 F.3d 901 (7th Cir. 2007); *Siharath*, 131 F. Supp. 2d 1347, 1361-62 (N.D. Ga. 2001).

All involved experts who had little to no epidemiology to support their opinions, and limited-quality case reports. In *Allison v. McGhan*, there were 20 epidemiological studies, but they all failed to show an association between the drug and the event, and the expert was relying solely on case reports to support his opinion. 184 F.3d 1300 (11th Cir. 1999). This is not the case with Dr. Leffler.

Defendants take issue with Dr. Leffler performing a differential diagnosis on the MedWatch reports, claiming that he has substituted a differential diagnosis for general causation. Def. Brief at 36. As noted above, Dr. Leffler's differential diagnosis, and review of, the MedWatch reports "support[ed his] conclusion that olmesartan causes enteropathy," it was not the sole basis of that conclusion. Furthermore, the MedWatch reports reviewed by Dr. Leffler are of a much higher quality that those referenced in the cases cited by Defendants, in that they all involved rechallenges.

Dr. Kessler's methodology for selecting MedWatch reports is clear and reproducible. The 60 MedWatch cases were selected from the large universe of adverse events produced by Daiichi because they described diarrhea, vomiting or celiac disease symptoms that were also both serious and included a rechallenge. Ex. 53 - Kessler Letter (Ex. 23 to Leffler Dep.); Ex. 39 at 17; Ex. 54 - Hutfless Dep. at 67:17-68:4, 105:12-106:5, 175:17-176:2. Dr. Leffler took the further step of confirming Dr. Kessler's selection criteria to ensure that they were appropriate to

identify cases of olmesartan enteropathy. Ex. 2 at 353:12-17. Defendants don't and can't challenge that the 62 MedWatch forms satisfied the criteria selected by Plaintiffs' experts.

Dr. Leffler applied the Naranjo criteria to these MedWatch reports. *Id.* at 329:25-332:10. He spoke with Dr. Hutfless about the MedWatch forms with fields for comorbid medical conditions, medication and allergies that had been coded as "not mentioned" by his team. Ex. 54 at 430:19-431:5; 431:22-432:5. Dr. Leffler clarified that the coding of "not mentioned" was equivalent to his determination that there was "no contribution for each of the categories. Ex. 54 at 430:21-431:5; see also 431:22-432:5. Dr. Leffler's review of the MedWatch reports was "fully consistent with [his] clinical experience and reading of the medical literature," and it "support[ed] his opinion that olmesartan causes enteropathy." Ex. 2 at 202:24-203:5; Ex. 1 at 14. It also is in line with methodology of reviewing the totality of the available evidence. This is a stark contrast from the approach of Defendants' experts, who reviewed only a limited subset of the published medical literature on the topic, and who didn't review any MedWatch reports. For these reasons, Defendants' arguments must fail.

CONCLUSION

For the foregoing reasons, this Court should deny Defendants' motion to exclude the testimony of Dr. Leffler.

Dated: April 21, 2017

Respectfully submitted,

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